Applicant: Ali I. FATTOM et al.

Title: GLYCOCONJUGATE VACCINES FOR USE IN IMMUNE-COMPROMISED POPULATIONS

Appl. No.: 09/955,585

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DECLARATION UNDER 37 CFR § 1.132

I, Ali Fattom, Ph.D., hereby declare and state as follows:

1. I am a citizen of the United States and an inventor of the captioned U.S. patent application, U.S. Patent Application Serial No. 09/955,585 (the "application").

2. I have a Ph.D. in microbiology and spent five and a half year at the National Institutes of Health studying bacterial pathogenesis and developing vaccines and immunotherapies against pathogenic bacterial infections. I worked under the supervision of Dr. John B. Robbins, one of the most prominent vaccinologists in the world, and gained first class experience in vaccinology of Gram positive organisms such as *pneumococcus* and *staphylococcus* and Gram negative bacteria such as *E. coli, Pseudomonas* and *salmonella.*

3. In 1991 I moved to a biotechnology firm in Rockville, Maryland, Univax Biologics, which is now Nabi Biopharmaceuticals, the assignee of the application. I am Vice President of Research, and my role is to develop innovative products. StaphVAX, a vaccine

against multidrug resistant *S. aureus*, is the lead product that has been developed by my group. The StaphVAX vaccine is a composition according to the claims of the application.

4. As an academician, I am involved in reviewing scientific work for publication in journals such as the Journal of Infectious Diseases, Vaccine, and others. I evaluate the scientific merit of these investigations, as well as their originality and significance.

5. I have published more than 45 papers and reviews in peer-reviewed journals and in reference books, as indicated in the list of publications attached to my CV (provided in Appendix A).

6. I have reviewed the Office Action mailed March 18, 2005 in connection with the application (the "Office Action") and submit this declaration in response to issues raised therein.

S. Aureus Infection

7. More than 85% of *S. aureus* infections are caused by bacteria strains carrying the Type 5 and Type 8 capsular polysaccharides. These capsules are antiphagocytic, enabling the bacteria to persist in the blood. They elaborate several virulence factors, including toxins and extracellular enzymes.

8. Clearance of these Gram-positive bacteria from the blood is through the mechanism of opsonophagocytosis. See, e.g., Karakawa et al., Infect. Immun. 56: 1090-95 (1988).[1] Opsonophagocytosis requires the presence of type-specific antibodies, complement, and polymorphonuclear leukocytes (PMN).

[1] All references are included in Appendix B in order of citation.

ESRD Patients Are Representative of Immune Compromised Patients

9. Immune compromised patients are patients who have deficiencies in one or more aspects of their immune systems, such as deficiencies of complement components, decreased phagocyte number and/or function (including neutropenia), impaired antibody production, or combined defects. See, e.g., Janoff & Rubins, Clin. Infect. Dis. 29: 289-91 (1999).

10. ESRD patients typically exhibit a number of defects in their immune systems, including (i) depressed neutrophil function and impaired phagocytosis; (ii) leukopenia secondary to complement activation as a result of dialysis; (iii) reduced natural killer cell activity; (iv) decreased T and B lymphocyte activity; and (v) decreased T lymphocyte response to standard antigens. See, e.g., Lewis et al., Am. J. Kidney Dis. IX: 381-95 (1987); Minnaganit & Cunha, Infect. Dis. Clin. N. Am. 15: 385-406 (2001).

11. The Office Action asserts that ESRD patients have competent T-cell and B-cell systems, but that assertion is contrary to the understanding in the art that ESRD patients with uremia have decreased T and B lymphocyte function. See, e.g., Lewis et al., supra at page 386.

12. ESRD patients on hemodialysis typically have the most severely compromised immune systems. ESRD patients exhibit sub-functional complement activity as a result of repeated dialysis and the interfacing between blood and membranes used in dialysis. See, e.g., Vanholder et al., Nephron. 63: 409-15 (1993). As set forth in the Abstract of Lewis et al., supra, "studies involving the HD [hemodialysis] patients showed that there is a decreased PMN in vitro chemotactic response, decreased C5a receptors on both PMNs and monocytes, and decreased

oxidative metabolic responses of PMNs and monocytes to the chemotactic stimuli C5a and formyl-met-leu-phe (fMLP)."

13. Most ESRD patients on hemodialysis are elderly, many are diabetic, and they routinely suffer from uremia. Uremia and hyperglycemia (e.g., diabetes) have a further debilitating impact on the immune system, particularly via impaired complement and phagocytosis. For example, Minnaganit & Cunha, supra at page 385, note that "[t]he presence of a substantial impairment of immunity in patients with uremia has been well-documented." They explain further, "maintenance hemodialysis (HD) can alter neutrophil function, reduce the ability for phagocytosis, depress natural killer cell activity, and can alter T and B cell function."

14. Because ESRD patients exhibit a number of deficiencies in their immune system, they are representative of immune compromised patients generally, including elderly patients (i.e., patients aged 55 and older), diabetic patients, and patients with invasive surgical procedures (including patients with vascular graft access and implants). As explained above, ESRD patients exhibit reduced opsonophagocytic activity. Diabetic patients and the elderly exhibit the same type of immune deficiencies. For example, Mazade & Edwards, Molec. Gen. & Metab. 73: 259-67 (2001), reported that diabetes patients exhibit inefficient opsonophagacytosis by neutrophils, and Romero-Steiner et al., Clin. Infect. Dis. 29: 281-88 (1999), reported that elderly patients exhibit reduced opsonophagocytic activity. Patients undergoing invasive surgical procedures, such as hip and knee replacements, often are also elderly. Thus, ESRD patients, the elderly, diabetic patients, hemodialysis patients, and patients with uremia all may exhibit inactive complement and ineffective neutrophils. Thus, the immune deficiencies exhibited by ESRD

patients are similar to the immune deficiencies exhibited by other immune compromised patient populations, and ESRD patients are representative of immune compromised patients generally.

Difficulties In Vaccinating Immune Compromised Patients

15. Vaccines that are immunogenic in healthy patients have been found to be less immunogenic or nonimmunogenic in immune compromised patients. For example, the immune response of hemodialysis patients to the hepatitis B vaccine was shown to be only 50-80% of the response observed in healthy patients. See, .e.g., Pirofski & Casadevall, Clin. Microbiol. Rev. 11: 1-26 (1998). The response of elderly patients to the vaccine was reduced to 46%. Id. While licensed (approved) vaccines are currently recommend for use in high-risk, immune compromised patients, clinical use has shown that the vaccines generally perform poorly in such patient populations. Id.

16. Romero-Steiner et al., supra, compared the responses of elderly patients and younger adults to a 23-valent polysaccharide vaccine against *Streptococcus pneumoniae*. The 46 elderly patients were previously unvaccinated, healthy, institutionalized persons with a mean age of 85.5 years. The 12 healthy younger adults had a mean age of 37 years. The investigators measured pre-vaccination and post-vaccination serum IgG antibody concentrations by ELISA, functional antibody activity by opsonophagocytosis, IgG antibody avidity, and passive protection in mice. As reported in the Abstract, post-vaccination IgG antibody concentrations for two serotypes (6B and 19F) of the five studied (4, 6B, 14, 19F, and 23F) were significantly lower in the elderly than in the younger adults. Moreover, opsonophagocytic activity was significantly

reduced for all serotypes in the elderly. Sera with reduced opsonophagocytic activity (titer <64) correlated with low IgG antibody avidity and protected mice poorly against pneumococcal challenge. In elderly persons receiving polysaccharide vaccination, there was a significant reduction in the functionality of post-vaccination antibodies, which appeared to increase with advanced age. As the investigators conclude at page 287, "this study highlights the importance of evaluating the IgG antibody response, as well as the functional antibody activity of the antibodies measured, especially in high-risk populations."

17. Most post-licensure vaccine studies focus on surrogate markers of immune response determined in healthy, immune competent patients. For example, after the introduction of the Hemophylus influenzae type B vaccine, infection rates were reduced to levels that made new studies based on infection rates impossible. The FDA therefore decided to evaluate new vaccines on the basis of a surrogate marker. Because there was an established correlate of protection (0.15 μg/ml capsular polysaccharide-specific antibodies), new vaccines are evaluated on the levels of antibodies they induce as compared to those induced by the licensed vaccine.

18. I was a member of the forum assembled by the FDA to discuss the use of surrogate markers to evaluate vaccine efficacy for the Gram positive pathogen Group B Streptococcus (GBS). The consensus reached by the forum was that you need to both measure induced antibody level and evaluate efficacy by functional tests. The forum members realized that a vaccine's ability to induce antibodies is not sufficient to demonstrate efficacy, and that a functional assay, such as an assay to measure bactericidal activity (in the case of Gram positive organisms) or opsonophagocytosis (in the case of GBS and *Staphylococci*) is required.

Moreover, the consensus view is that the use of surrogate markers is acceptable only when clinical trials are not feasible, or where a well-established surrogate marker is available.

19. The relevancy of surrogate markers to efficacy in immune compromised patients has not been established. See, .e.g., Pirofski & Casadevall, supra at 19. Thus, the ability of a vaccine to induce antibody levels that would be protective in a healthy patient has not been shown to correlate with protection in immune compromised patients. Id. Even if the same antibody levels are induced in immune compromised patients, protection may not be achieved. For example, impaired effector cell function and deficiencies in nonspecific immune mechanisms (such as complement activation) may render the antibody-mediated immunity ineffective in immune compromised patients. Id. For example, Broome et al., N. Eng. J. Med. 303: 549-52, at 549 (1980), addressed the efficacy of pneumococcal vaccines in immunocompromised populations, and noted that "[t]he possibility that efficacy is low in high-risk, immunocompromised patients population makes it important to evaluate clinical efficacy and not just serum antibody responses in such groups."

20. In view of these art-recognized difficulties, the use of licensed vaccines in immune compromised patients continues to present challenges. As explained above, the efficacy of a vaccine in healthy patient populations is not predictive of efficacy in immune compromised patients. Moreover, the ability of a vaccine to induce antibody levels that would be protective in healthy patients is not predictive of protection in immune compromised patients. Thus, the development of a vaccine that is effective in immune compromised patients is

unpredictable, even if the vaccine has proven efficacy in healthy patients or has been shown to induce high antibody levels in immune compromised patients.

21. We encountered these difficulties in developing the method of this patent application. An early clinical trial of a bivalent vaccine including glycoconjugates of Type 5 and Type 8 antigens failed to show efficacy in ESRD patients. The trial was a Phase 2 clinical trial that we conducted to assess the efficacy of a formulation containing type 5 and type 8 antigens, each of which were conjugated to *r*EPA. A randomized, double-blind, placebo-controlled design was utilized, and the trial was conducted at 23 academic or academic-affiliated dialysis centers throughout the U.S. Adult patients were stratified by the presence or absence of *S. aureus* nasal carriage. The primary endpoints were the frequencies of *S. aureus* peritonitis and all *S. aureus* dialysis-related infections (peritonitis plus catheter and/or catheter tunnel infections) in one year of follow-up after immunization.

22. The trial was initiated in August of 1993. A total of 237 subjects were randomized to the vaccine or placebo treatment in a ratio of 1:1. One hundred twenty (120) received 23 μg of type 5 conjugate and 13 μg of type 8 conjugate in a single 0.5 mL IM dose of vaccine; 117 received an equivalent volume of saline placebo. Two hundred five (205) subjects completed the trial. Twenty-three (23) were lost to death and nine were lost to follow-up for other reasons (these losses were approximately equally distributed between the treatment groups). All 237 subjects were included in the analysis.

23. There were no significant differences between the treatment groups in age, gender distribution, baseline Karnofsky score, baseline rate of *S. aureus* nasal carriage, or prevalence of diabetes mellitus. There was no evidence of vaccine-related safety concerns.

24. The primary efficacy analysis revealed no effect on the frequencies of *S. aureus* peritonitis or all *S. aureus* dialysis-related infections. Other infections due to *S. aureus* were too infrequent to permit meaningful analysis. Thus, the clinical trial did not demonstrate that the vaccine could protect immune-compromised individuals from infection.

25. Despite this failure, we continued our work to develop a method of protecting immune compromised patients from *Staphylococcal* infection. Although nothing in the art suggested that a higher vaccine does would resolve the lack of efficacy, we planned another trial using higher vaccine doses (100 μg/mL (+/- 20%) of each of the Type 5 and Type 8 antigens). That trial was successful, as reported in the application, and as explained in more detail below.

The Efficacy of Our Vaccine In Immune Compromised Patients

26. Example 2 at pages 16-20 of the application describes the successful clinical trial of our vaccine (StaphVAX) in immune compromised patients, and shows that we have invented a method of protecting immune compromised patients from *Staphylococcal* infection. As presented in the application, the data demonstrate protection in ESRD patients. As explained above, ESRD patients are representative of immune compromised patients generally because they typically exhibit a number of deficiencies in their immune systems. For that reason, once a vaccine has been shown to be effective in ESRD patients, those skilled in the art would expect

the vaccine to be effective in other immune compromised patients, such as the elderly, diabetic patients, and patients with invasive surgical procedures. The data underlying Example 2 also directly establishes the efficacy of our method in elderly patients, diabetic patients, and patients with invasive surgical procedures, as explained below.

27. As noted at page 16 of the application, the mean patient age was 58.3 years. Out of the 1804 patients followed, 1,111 were aged 55 or older. While studies involving healthy elderly patients often use a higher age cut-off for "elderly," such as 65 years, when the patients have a co-morbid condition, such as ESRD, diabetes, or high blood pressure, a lower cut-off for "elderly" typically is used, such as 55 years. Thus, the data showing the efficacy of the vaccine directly demonstrates its efficacy in elderly patients because the patients studied were "elderly."

28. Moreover, looking at the data for patients over age 65 in the study shows that the vaccine is effective in those patients, and shows that we have invented a method of protecting elderly patients from *Staphylococcal* infection. At all times from weeks 3 through 54 post-vaccination, the cumulative number of patients with bacteremia was greater for the placebo group (8 vs. 11) than for vaccinated patients aged 65 and older. Through week 40, there were 6 bacteremias in the placebo group compared to only 3 in the aged 65 and older StaphVAX group.

29. As noted at page 16 of the application, 52% of the StaphVAX group and 51% of the placebo group were diabetic. In total, 931 of the 1804 patients followed were diabetic. At all times from weeks 3 to 54 post-vaccination, the cumulative number of patients with bacteremia was greater for the diabetic placebo group than for the diabetic StaphVAX group. Through week 39, there were 15 bacteremias in the diabetic placebo group compared to only 7 in the diabetic

StaphVAX group. Through week 40, there were 16 bacteremias in the diabetic placebo group compared to only 8 in the diabetic StaphVAX group.

30. As noted at page 16 of the application, 69% of the subjects in both the StaphVAX and placebo groups had vascular graft access (i.e., had undergone invasive surgical procedures). Indeed all of the patients had some type of vascular access, either with grafts or fistulas. Thus, the data reported in the specification demonstrates the efficacy of the invention in patients who have undergone invasive surgical procedures.

31. In addition to the study reported in the application, we have conducted a study in rabbits to confirm the efficacy of our method to prevent *Staphylococcal* infection in patients who have undergone the invasive surgical procedure of receiving an orthopedic implant. Patients undergoing total knee arthroplasty (TKA) are at a high risk for *Staphylococcal* infection. We used a rabbit knee model to investigate the efficacy of StaphVAX in this population of immune compromised patients. All animals in the StaphVAX group achieved an antibody titer at least 10-fold higher than baseline, and animals in the StaphVAX group demonstrated a significant decreased incidence of infection compared to controls. This study is reported in Craig et al., Orthoped. Res. Annual Mtg (2004).

The Clinical Trial of Our Vaccine In Immune Compromised Patients

32. The study reported in the application is based on a phase III clinical trial of our vaccine in immune compromised patients. The clinical trial was designed by Nabi (now "Nabi Biopharmaceuticals"), the assignee of the application, and was conducted under the direction and

control of Nabi. The clinical trial was a randomized, placebo-controlled, double-blind study. Investigators were required to sign confidentiality agreements and were required to sign an agreement stating that they would follow the detailed protocol designed by Nabi. Under the protocol, neither the investigators nor the patients knew whether a given patient received the vaccine or a placebo. Appendix C includes redacted pages excerpted from the clinical trial protocol.

I further declare that all statements made in this declaration of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of legal decisions of any nature based on them.

July 13, 2005
Date

Ali Fattom, Ph.D.